

MALARIA ANCIENT SCOURGE - STILL EVOLVING AND RELEVANT

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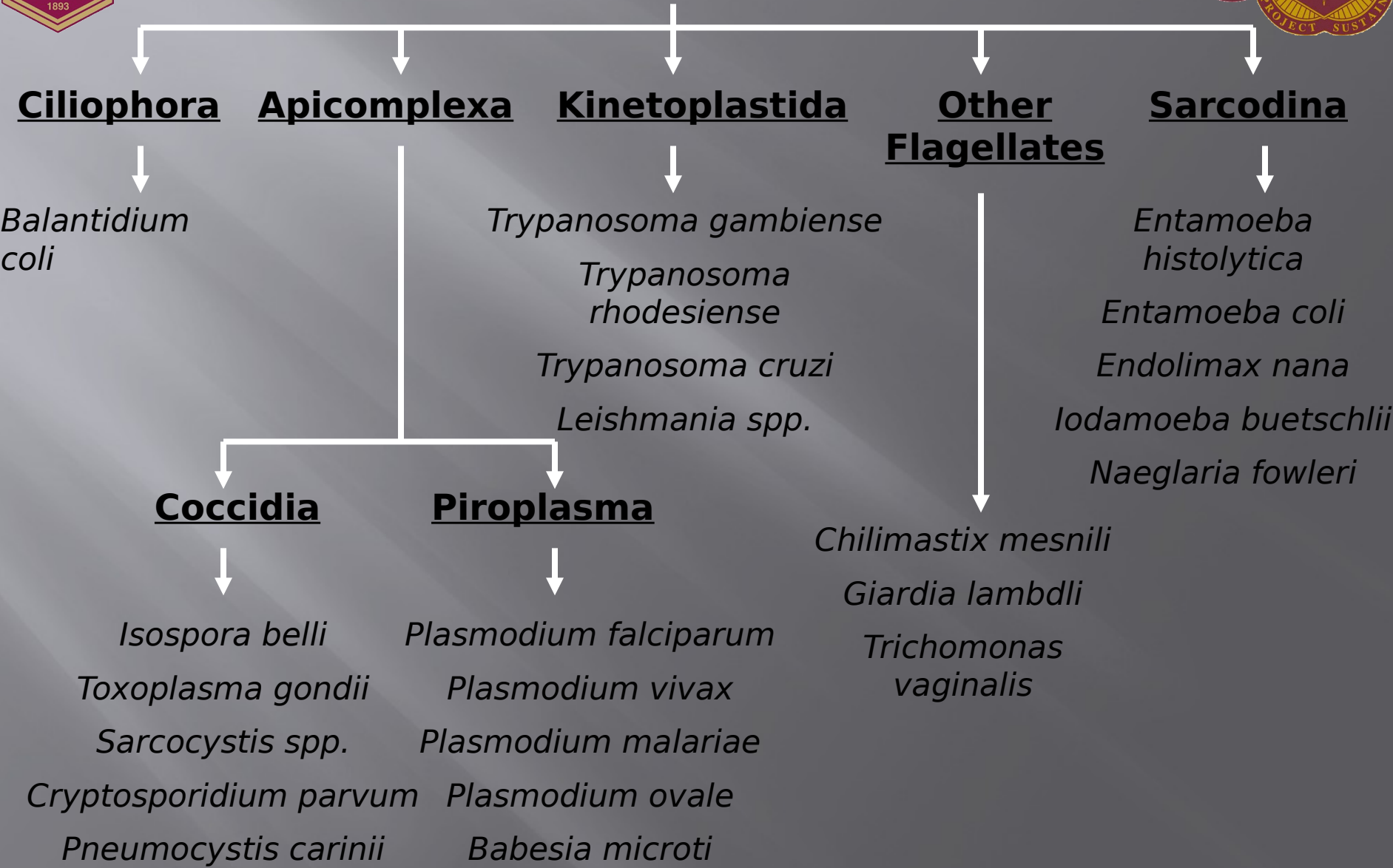
WRAIR

Walter Reed Army
Institute of Research

Soldier Health • World Health

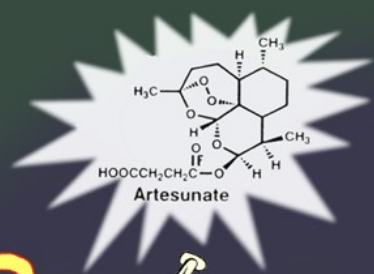


Protozoans





CPT Chemo ET vs Malaria



PRESENTS



R. Lee Collins,
MAVS

Heλλ Ψεο!!



History

- Chinese writings (2700 BC)
- The Eber's papyrus (1550 BC)
- Hippocrates (described malaria fevers)
- Greek civilizations affected by “bad air”, the rich summered in the highlands
- Malaria in the United States???
 - First military expenditure in 1775 (\$300) for quinine to protect G. Washington's troops
 - In Civil War (1861-65) 50% white and 80% of black troops w/ malaria annually



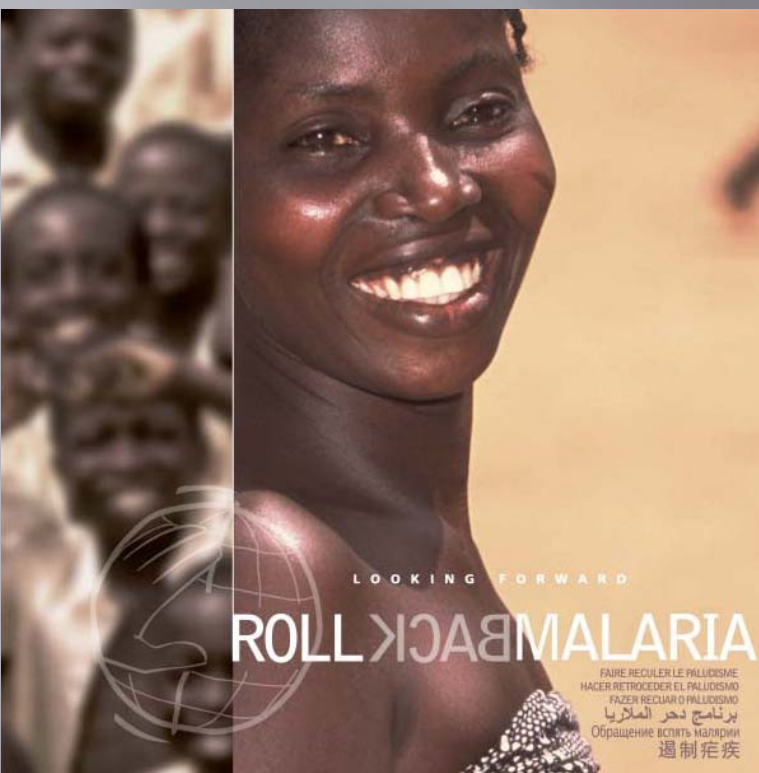
- 1880-Laveran made first sighting of parasite
- 1902-Ross awarded Nobel Prize (mosquito)
- 1927-Wagner von Jauregg awarded Nobel Prize for treating syphilis with malaria
- 1950-WHO plan for malaria eradication-1955
- mid-1960's, chloroquine-resistant *falciparum*
- Eradication effort declared dead in 1972



"Doctor, this will be a long war if for every division I have facing the enemy, I must count on a second division in hospital with malaria and a third division convalescing from this disease".

General Douglas MacArthur, May 1941
Colonel Paul F. Russell, MC, the American
army malaria consultant.





THE GLOBAL MALARIA ACTION PLAN
For a malaria-free world

- Roll Back Malaria launched in '98 (WHO, UNICEF, UNDP & World Bank)
- Halve malaria by 2010; Eliminate malaria in 8-10 countries by 2015



on of malaria



Malaria

Ancient & Worldwide Impact

- Most important parasitic disease affecting man
- ~ 515 million cases of malaria in 2002 *
- 189 - 327 million cases of malaria in 2006#
- ~1.5 to 2.7 million deaths per year (2002)*
- 610K - 1.2 million deaths per year (2006)#
 - 90% of all deaths occur in Africa
 - The majority occur in children < the age of 5
- 2.2 billion people at risk worldwide in 2002 *
- 3.3 billion people were at risk of malaria in 2006#

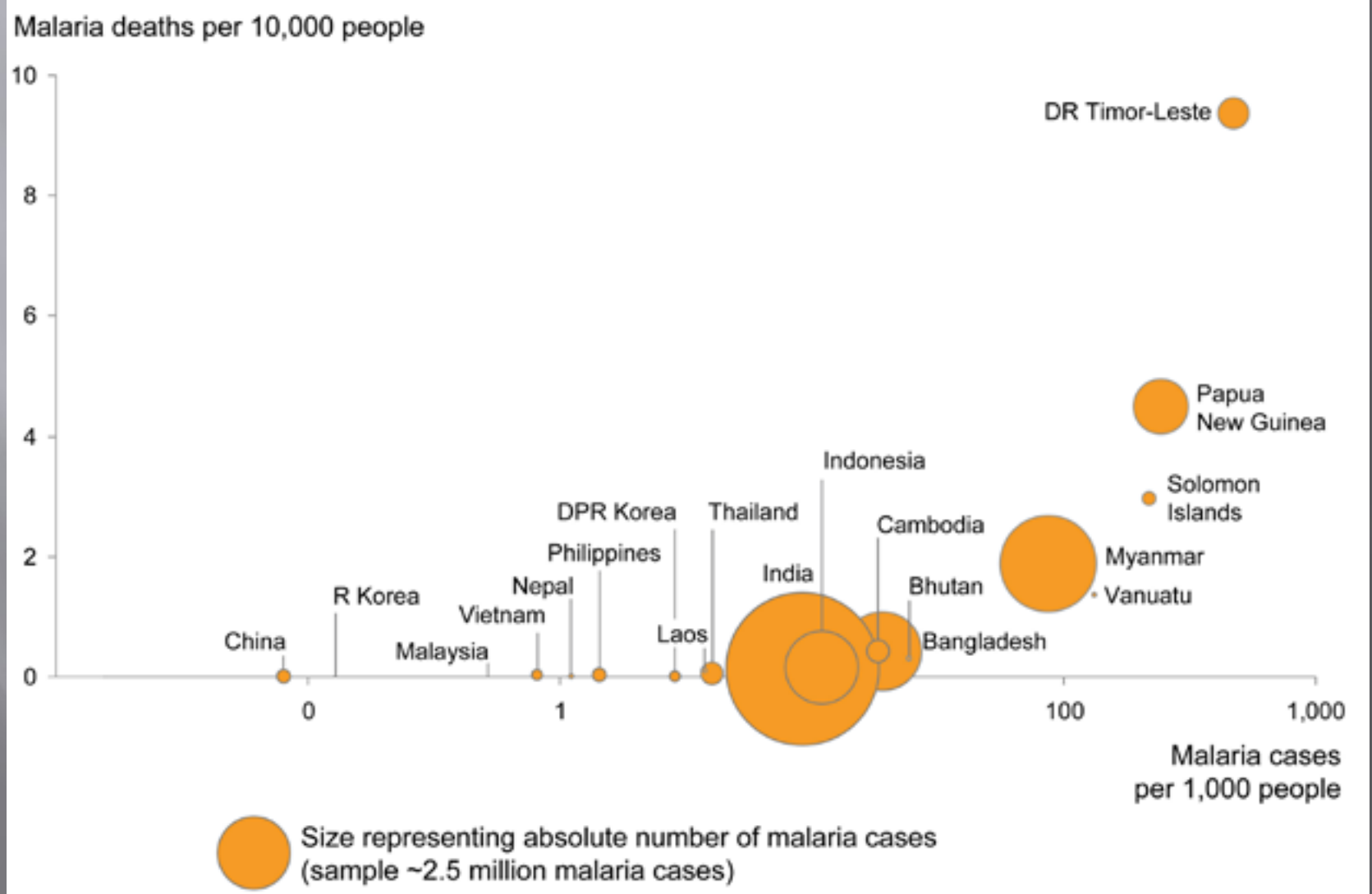
* Snow et al.; Nature 2005 Mar 10; 434(7030):214-7

<http://www.who.int/malaria/wmr2008/malaria2008.pdf> (2008)



Malaria

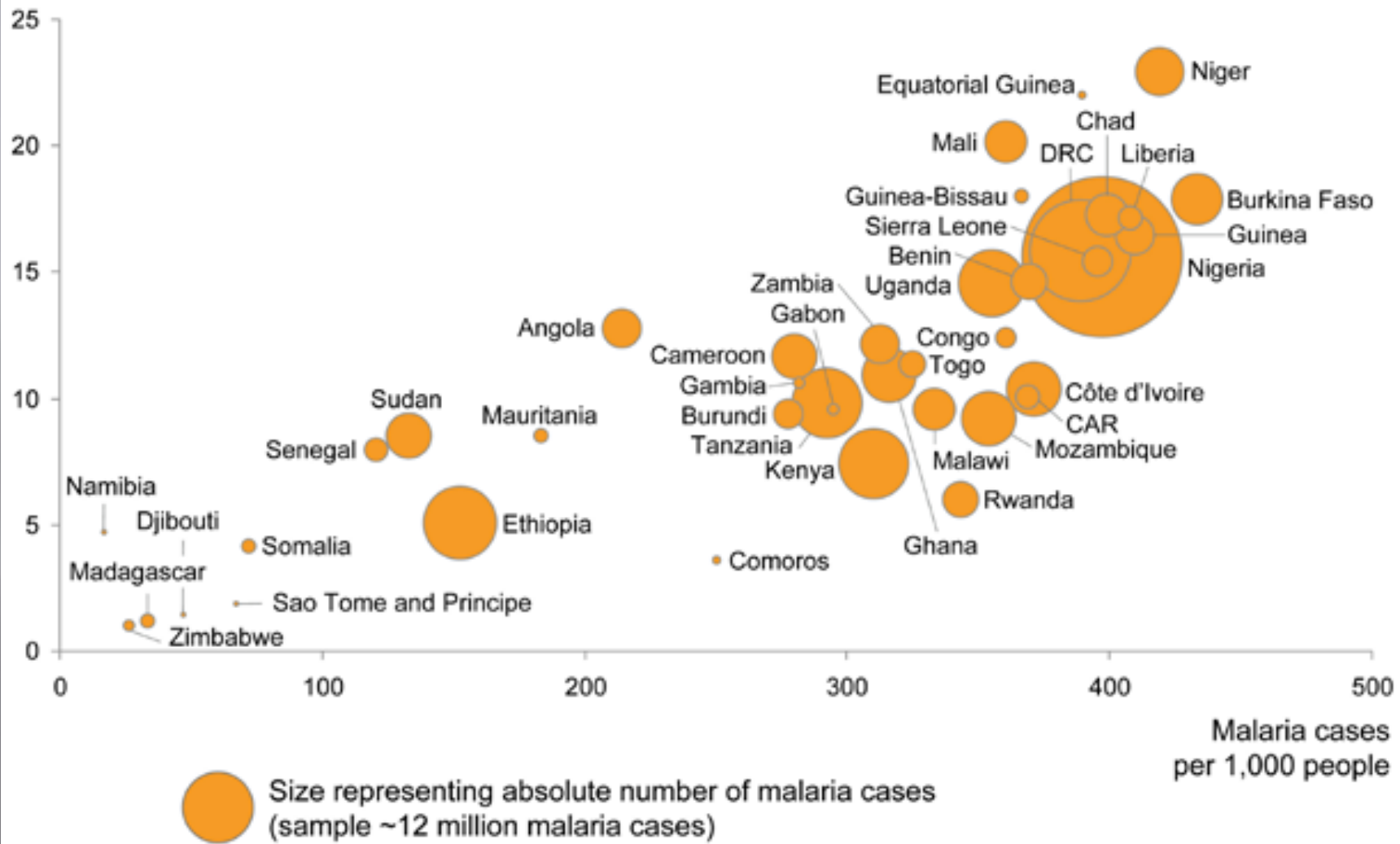
Impact in Southeast Asia





Malaria Impact in Africa

Malaria deaths per 10,000 people







Destabilization Effect

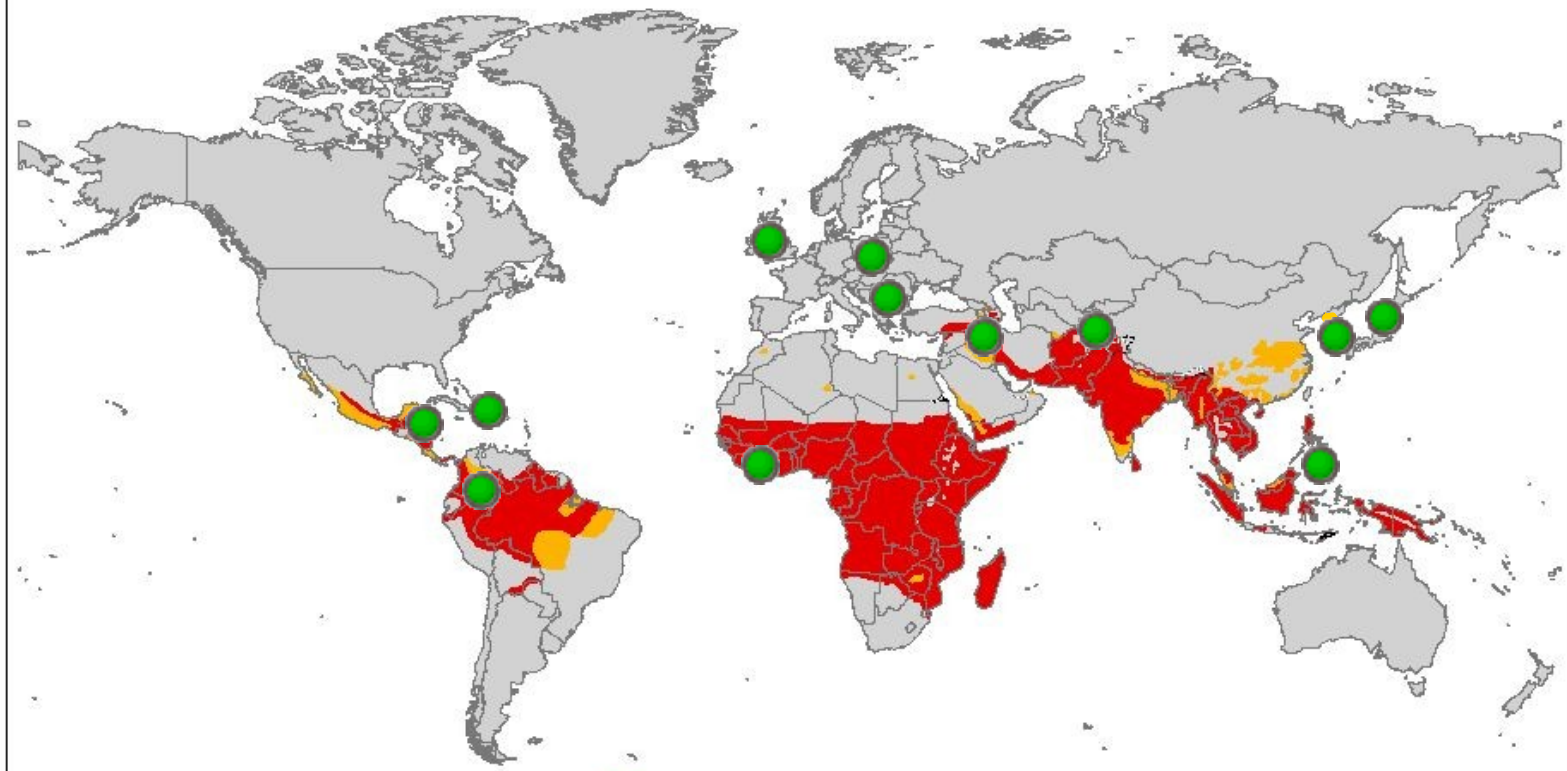


- There are huge impacts of HIV/AIDS, malaria, and MTb on the critical infrastructures that sustain the security, stability, and viability of modern nation-states
- In the developing world (esp Africa) these diseases undermine education and health systems, economic growth, micro enterprises, policing and military capabilities, political legitimacy, family structures, and overall social cohesion
- Undermine the stability of already weakened states, adds to their vulnerability to extremists/terrorists who will seek to corrupt or coerce them into providing converts, cover, or cooperation
- The real global war can be thought of being against these diseases - needs to be comprehensive, fought at many levels and on many fronts






Worldwide Malaria Distribution

Worldwide malaria distribution in 2002



 **US Troops Worldwide**

-  Areas where malaria transmission occurs
-  Areas with limited risk
-  No malaria



The presentation of material on the maps contained herein does not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or areas or of its authorities, or concerning the delineation of its frontiers or boundaries.



Data Source: WHO / RBM
Map Production:
Public Health Mapping Group
Communicable Diseases © WHO
World Health Organization, November 2002



Recent Military History



- US / Somalia 1992-3 (233 cases; 77% *P. vivax*)
- US Army 1995-2002
 - 30-75 cases/yr;
 - ~ 75% *P. vivax*
- US/ Afghanistan 2002 (38 cases)
- US / Liberia 2003 (80 cases)
- US/ Afghanistan today (>100 cases/yr)
- US/ Haiti 2010 (10 cases)
- Liberia 2009 (multiple cases, 1 death)
- Liberia 2010 (7 cases)



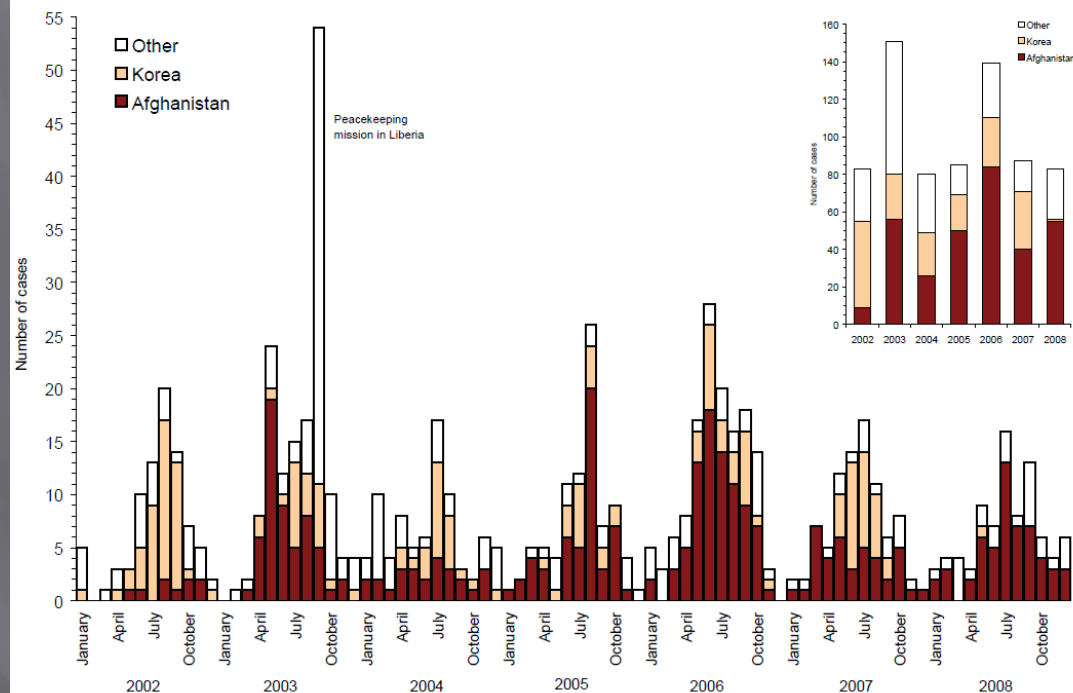
MSMR

A publication of the Armed Forces Health Surveillance Center



MEDICAL SURVEILLANCE
MONTHLY REPORT

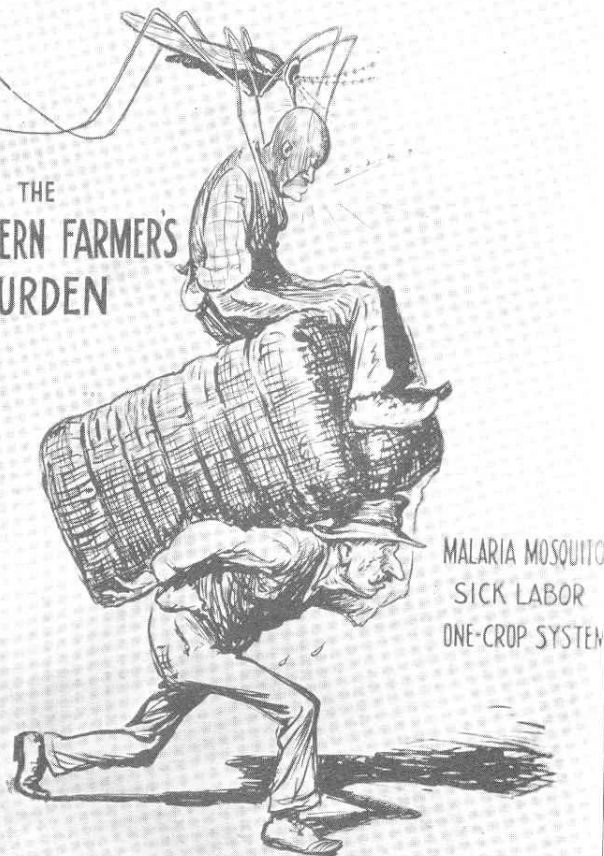
Figure 2. Malaria cases among U.S. service members, by estimated location of infection acquisition and month and year (inset) of clinical diagnosis/report, U.S. Armed Forces, January 2002-December 2008



Deaths and rates from malarial disease, white and colored.

Data taken from Mortality Report, National Board of Health, 1881, Bulletin of the Board, Vol. III, pp. 324-327.]

THE
SOUTHERN FARMER'S
BURDEN



	Population, 1880.		Deaths from malarial disease.		Ratio of deaths per 100,000 of living.		Ratio, 1880, white and colored. ¹	Ratio, 1917, white and colored. ²	Reduction for 37 years (per cent).
	White.	Colored.	White.	Colored.	White.	Colored.			
District of Columbia.....	120,000	60,000	78	84	65.0	140.0	90	1.4	98.4
Norfolk, Va.....	11,933	10,033	17	21	142.5	209.3	173	13.2	92
Richmond, Va.....	35,756	28,047	11	10	30.8	35.7	33	2.5	92.5
Lynchburg, Va.....	7,484	8,475	2	4	26.7	47.2	38		
Petersburg, Va.....	10,000	12,000	3	7	30.0	58.3	46	15.5	66
Wilmington, N. C.....	6,893	10,468	6	13	87.0	124.3	109	3.3	97
Charleston, S. C.....	22,712	27,287	9	9	39.6	33.0	36	36.0	
Augusta, Ga.....	12,364	10,659	6	5	48.5	46.9	48	31.6	34.2
Atlanta, Ga.....	21,086	16,335	5	3	23.7	18.3	21	1.5	93
Savannah, Ga.....	15,007	15,674	30	24	199.9	153.1	176	24.5	86
Mobile, Ala.....	16,837	14,368	19	11	112.8	76.6	96	23.6	75.4
Selma, Ala.....	3,345	4,184	8	22	239.1	525.8	398		
Columbus, Miss.....	2,760	2,470	1	2	36.2	81.0	57		
Natchez, Miss.....	3,421	3,637	2	1	58.5	27.5	43	33.9	21.2
Vicksburg, Miss.....	5,975	5,839	19	20	318.0	342.5	330	77.7	76.6
New Orleans, La.....	158,379	57,761	237	119	149.6	206.0	164	3.4	98
Shreveport, La.....	3,739	7,278	16	27	428.0	371.0	390	37.8	90.5
Baton Rouge, La.....	2,917	4,300	5	7	171.4	162.8	166	11.4	93
Galveston, Tex.....	16,900	5,353	10	5	59.2	93.4	67	2.3	96.5
San Antonio, Tex.....	17,525	3,036	12	2	68.5	65.9	68	16.4	76
Nashville, Tenn.....	27,004	16,457	11	15	40.7	91.1	60	5.9	90.3
Memphis, Tenn.....	18,622	14,971	20	27	107.4	180.3	140	36.9	73.8
St. Louis, Mo.....	328,232	22,290	345	42	105.1	188.4	110	1.7	98.5
Total and average.....	868,891	360,922	872	480	100.4	133.0	110	80.5

¹ This column added by Dr. T. H. D. Griffiths.

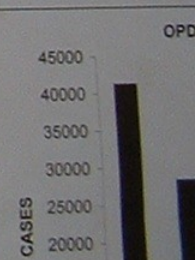
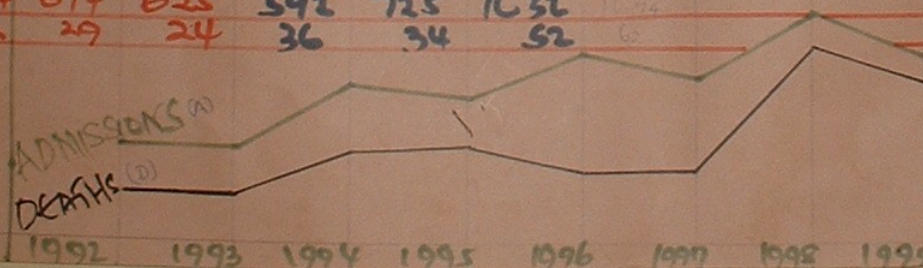
² 1917 report, Bureau of the Census.



IN-PATIENT MALARIA CASES - KISII DIST. HOSPITAL ONLY

YEAR	JAN	FEB	MAR	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC	TOTAL
1992	105	231	324	330	804	1180	1001	696	676	287	276	336	6846
	33	15	9	30	13	25	38	30	5	6	10	15	229
1993	352	587	476	359	379	436	1258	1261	398	370	416	402	6694
	18	12	26	15	22	14	22	34	22	10	10	23	228
1994	860	645	964	1087	1501	1776	2001	967	483	473	385	220	11352
	16	22	19	25	30	64	81	30	27	60	20	16	410
1995	835	804	375	545	1012	1004	1444	667	631	550	656	741	9258
	28	34	28	37	41	39	51	43	37	26	17	21	402
1996	834	1058	1459	2096	2106	1400	877	551	437	610	377	13124	
	38	39	18	25	26	45	16	6	28	14	18	12	275
1997	684	548	885	968	1312	2808	1837	942	548	520	267	STRIKE	11319
	21	34	27	37	28	46	48	25	26	32	18		342
1998	1065	4634	4820	1752	574	644	683	388	321	350	436	611	16218
	13	122	134	122	98	101	82	32	14	22	25	35	800
1999	571	433	562	569	1693	2615	2714	957	530	415	422	570	12051
	27	27	30	44	105	125	134	71	50	37	27	31	708
2000	736	648	646	651	805	923	1049	700	483	413	423	536	
	38	34	27	37	31	20	47	32	17	14	19	31	
2001	960	939	852	567	557	875	796	751	455	422	510	466	
	39	40	27	24	13	11	27	21	22	17	20	19	
2002	1094	674	625	592	725	1632	1694						
	22	29	24	36	34	52	65						

ADMISSIONS (A)
DEATHS (D)



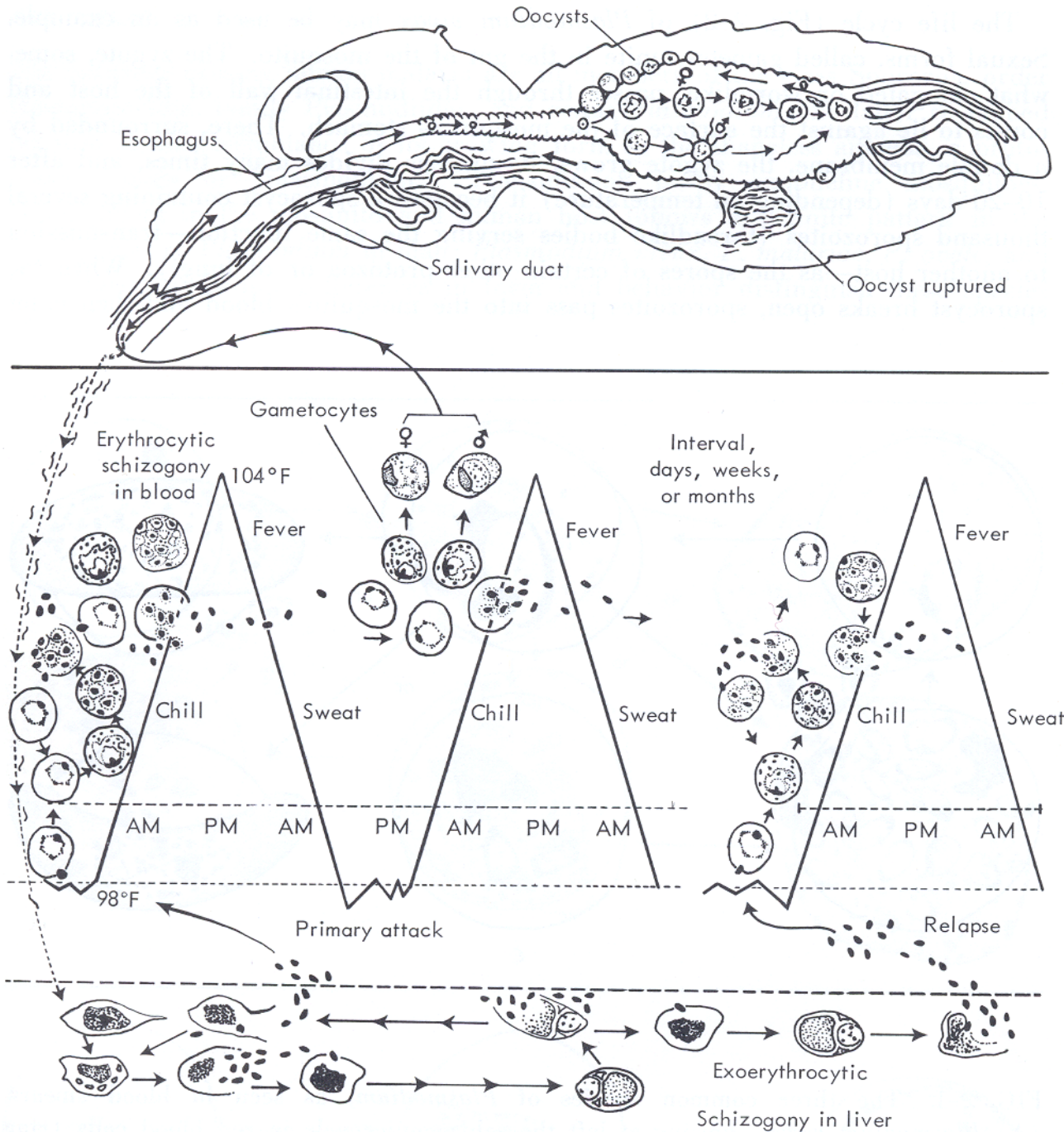






Malaria Parasites and Their Life Cycles

- Four human forms of malaria
 - *Plasmodium vivax*
 - 48h cycle, young RBCs, worldwide
 - *Plasmodium malariae*
 - 72h cycle, older RBCs, worldwide
 - *Plasmodium ovale*
 - 48h cycle, young RBCs, Africa
 - *Plasmodium falciparum*
 - 48h cycle, all RBCs, Tropical regions





Prepatent & Incubation Periods (parasites in blood vs. illness)

SPECIES	PREPATENT PERIOD	INCUBATION PERIOD
<i>P. falciparum</i>	11 - 14 days	8 - 15 days
<i>P. vivax</i>	11 - 15 days	12 - 20 days
<i>P. ovale</i>	14 - 26 days	11 - 16 days
<i>P. malariae</i>	21 - 28 days	18 - 40 days



The 5th Human Malaria

MAJOR ARTICLE

Plasmodium knowlesi Malaria in Humans Is Widely Distributed and Potentially Life Threatening

Janet Cox-Singh,¹ Timothy M. E. Davis,⁴ Kim-Sung Lee,¹ Sunita S. G. Shamsul,¹ Asmad Matusop,² Shanmuga Ratnam,³ Hasan A. Rahman,⁵ David J. Conway,⁶ and Balbir Singh¹

¹Malaria Research Centre, Faculty of Medicine and Health Sciences, University Malaysia Sarawak, and ²Sarawak Health Department, Kuching, and ³Disease Control Unit, Sabah Health Department, Kota Kinabalu, Malaysian Borneo; ⁴School of Medicine and Pharmacology, Fremantle Hospital, University of Western Australia, Fremantle; ⁵Pahang State Health Department, Kuantan, Malaysia; and ⁶London School of Hygiene and Tropical Medicine, London, United Kingdom

(See the editorial commentary by White on pages 172–3)

Background. Until recently, *Plasmodium knowlesi* malaria in humans was misdiagnosed as *Plasmodium malariae* malaria. The objectives of the present study were to determine the geographic distribution of *P. knowlesi* malaria in the human population in Malaysia and to investigate 4 suspected fatal cases.

Methods. Sensitive and specific nested polymerase chain reaction was used to identify all *Plasmodium* species present in (1) blood samples obtained from 960 patients with malaria who were hospitalized in Sarawak, Malaysian Borneo, during 2001–2006; (2) 54 *P. malariae* archival blood films from 15 districts in Sabah, Malaysian Borneo (during 2003–2005), and 4 districts in Pahang, Peninsular Malaysia (during 2004–2005); and (3) 4 patients whose



Plasmodium knowlesi

- Simian species of malaria naturally infecting macaques in Southeast Asia
- Resembles human species by microscopy
 - *P. malariae* (affects any age cell like *P. falciparum*)
- 24 hour replication cycle
 - Can cause severe and fatal infections
- Large numbers of human cases reported initially from Malaysian Borneo
- Subsequent reports of human cases in Peninsular Malaysia, Singapore, and the Philippines



Anopheline Mosquitos



- 50->80 species capable of transmission
- <40 really important
- Female requires blood meals for egg broods



Anopheline Mosquitos

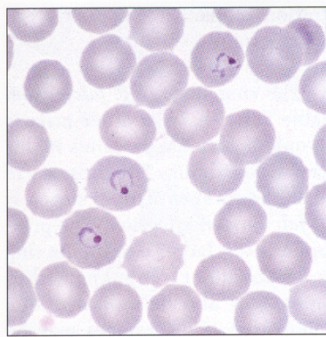
- Life cycle – 7 to 20 days (egg to adult)
 - egg -> larva -> pupa -> adult
 - Females mate once and lay 200-1000 eggs in 3-12 batches over a lifetime
 - Find their host by chemical and physical stimuli
 - Average life span of mosquito < 3 weeks
- Malaria development – 7 to 12 days
 - Each male & female gametocyte produce >10,000 sporozoites



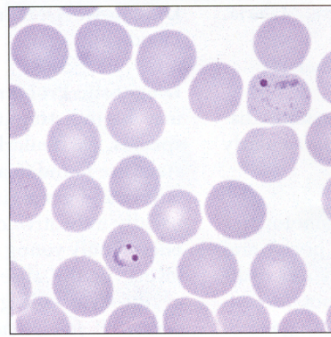


Diagnosis

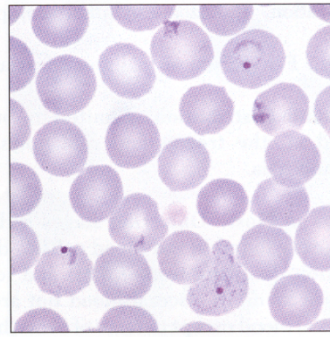
- Gold standard – Giemsa thick & thin smears
 - Species and parasite density determined
 - Labor intensive, modest cost
 - False negative circumstances
 - Parasites not present in circulation
 - False positive circumstances
 - Parasites seen may not be the cause of fever in endemic areas (Kisumu example of misdiagnosis...)
 - In highly endemic areas, clinical diagnoses made



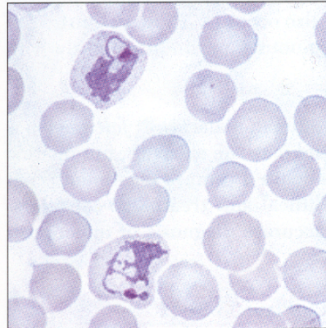
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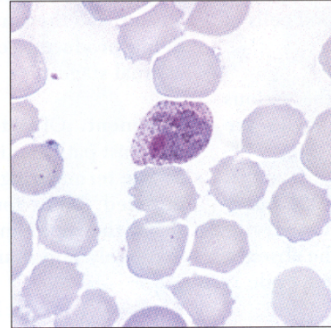
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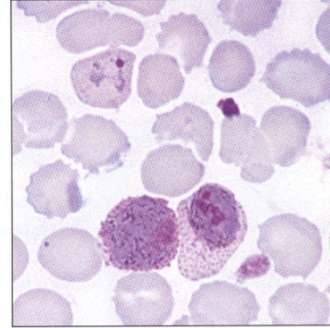
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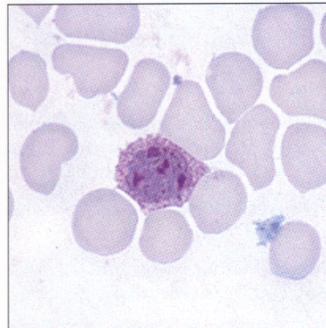
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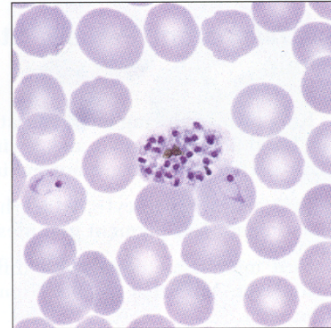
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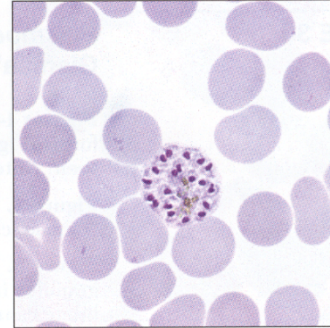
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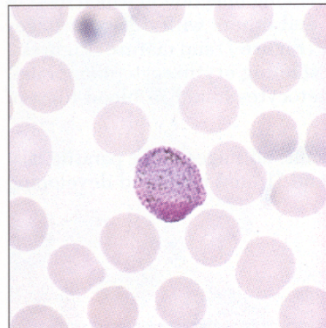
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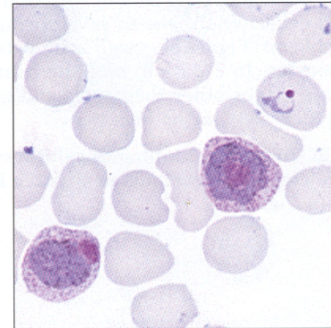
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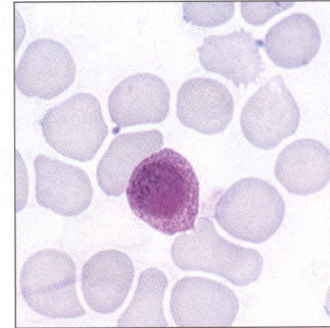
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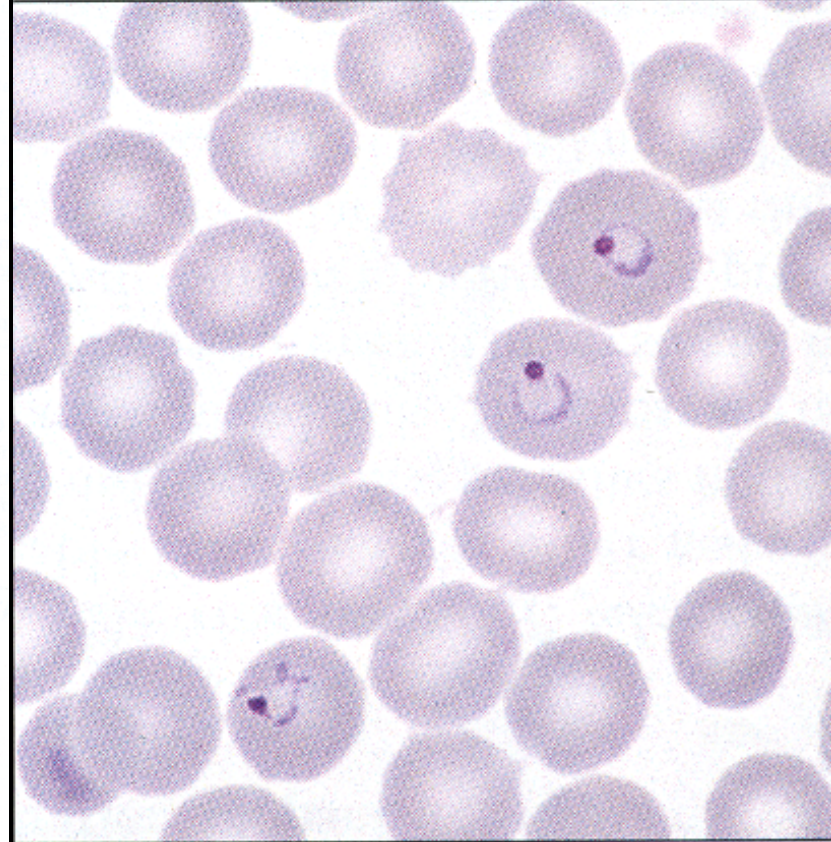
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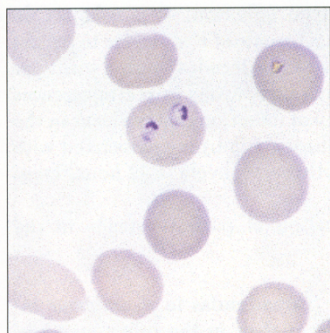
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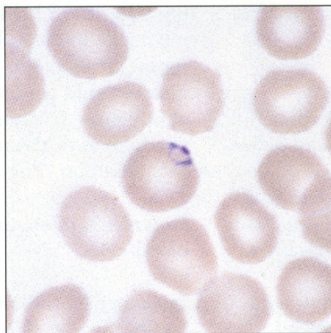
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*Plasmodium
vivax*



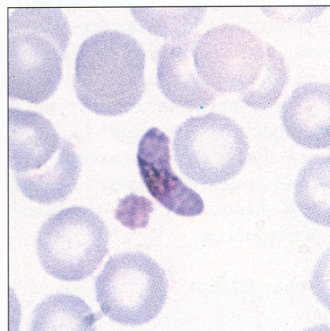
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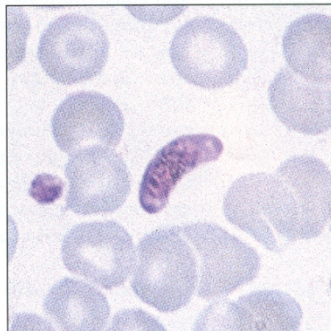
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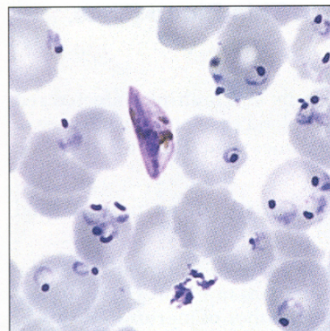
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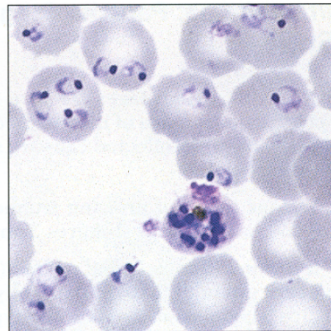
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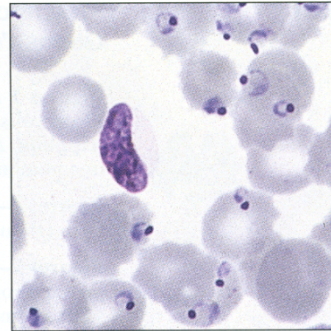
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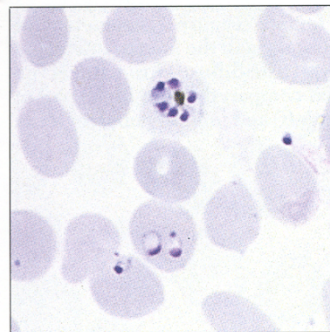
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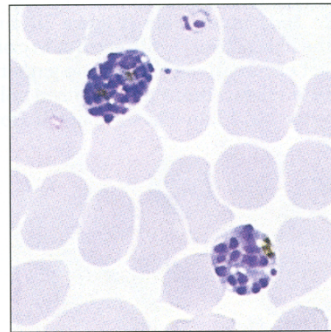
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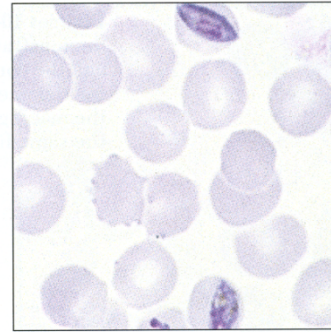
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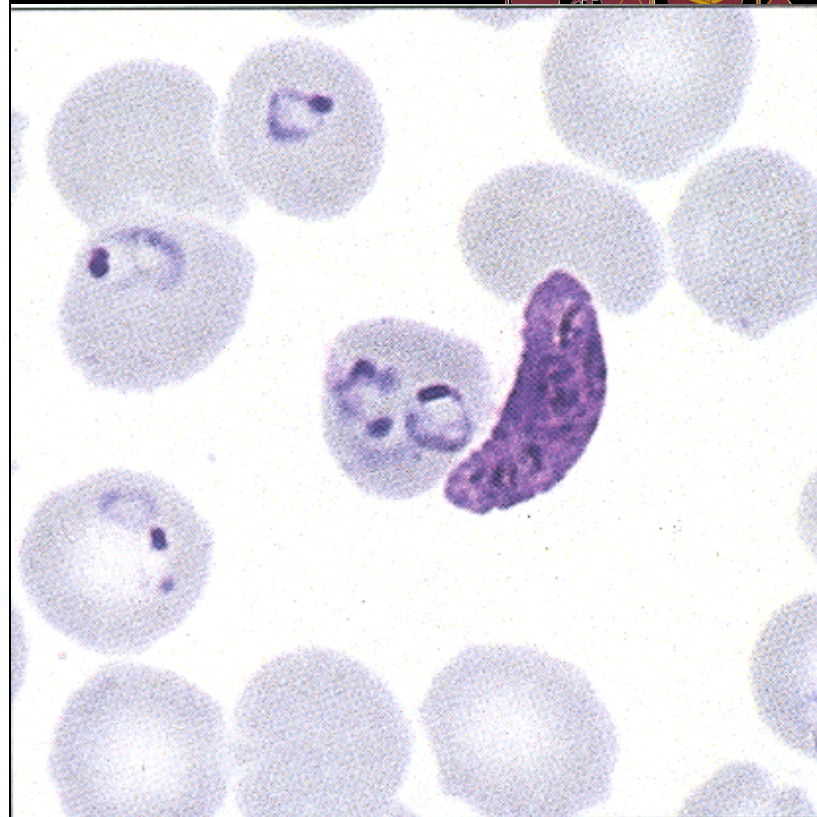
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12



*Plasmodium
falciparum*



Parasite Growth in the Blood

Log+ increase in parasites per 48-hour cycle (for *P. falciparum*)

Threshold	Parasite mia	Parasites/ml	Parasite burden
Expert Microscopy	0.0005%	20-50/ml	10^8 parasites
Symptoms in non-immunes	0.002%	100/ml	10^9 parasites
Malaria RDT	0.005%	100-1000/ml	10^{9-10} parasites
Severe malaria	2%	100,000/ml	10^{12} parasites
Death	10%	500,000/ml	10^{13} parasites

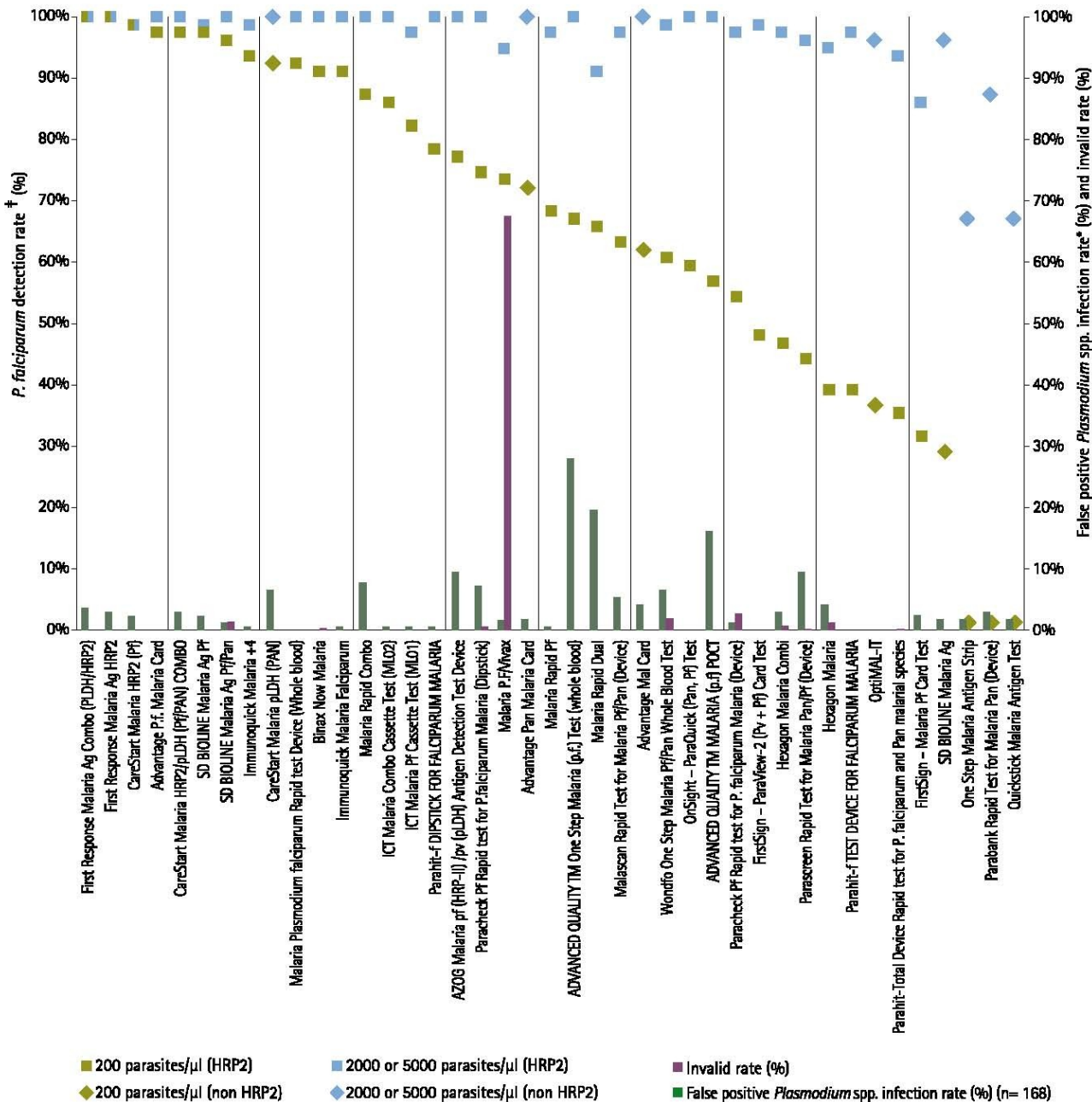


Rapid Diagnostic Tests

- Currently acceptable test(s)
 - *Binax Now*, Inverness Medical Innovations, Inc.
- Reliability
 - False negatives – Prozone Effect
 - Hyperparasitemia – too much antigen
 - HRP-2 assays (16/17) most affected; pLDH and aldolase not affected
- Follow-up
 - FDA ‘clearance’ Labeling – what does it actually say?



Figure E1: Summary performance of malaria RDTs against blood samples containing wild type *P. falciparum* at low (200) and high (2000 or 5000) parasite densities (parasites/ μ l) and malaria-negative samples.





NOW[®] ICT Malaria (Binax, Inc., Portland ME)



- Less than 15 minutes
- Non-microscopic
- Single reagent
- Minimally-trained operator
- Environmentally robust
- RDTs will NOT replace malaria microscopy
 - Confirmatory test for species, parasite density
 - Back-up to rule out inaccurate results



- *“Good doctors are useless without good discipline. More than half the battle against disease is fought not by doctors, but by regimental officers. It is they who see that the daily dose of mepacrine is taken, that shorts are never worn, that shirts are put on and sleeves turned down before sunset. . . I therefore had surprise checks of whole units, every man being examined. If the overall result was less than 95% positive, I sacked the commanding officer. I only had to sack three; by then the rest had got my meaning.”*

General Slim, Burma Campaign, WW II
(Under General Slim, the malaria rate in troops decreased from 12 per 1,000/day to 1 per 1,000/day)







Malaria Treatment US '2012'

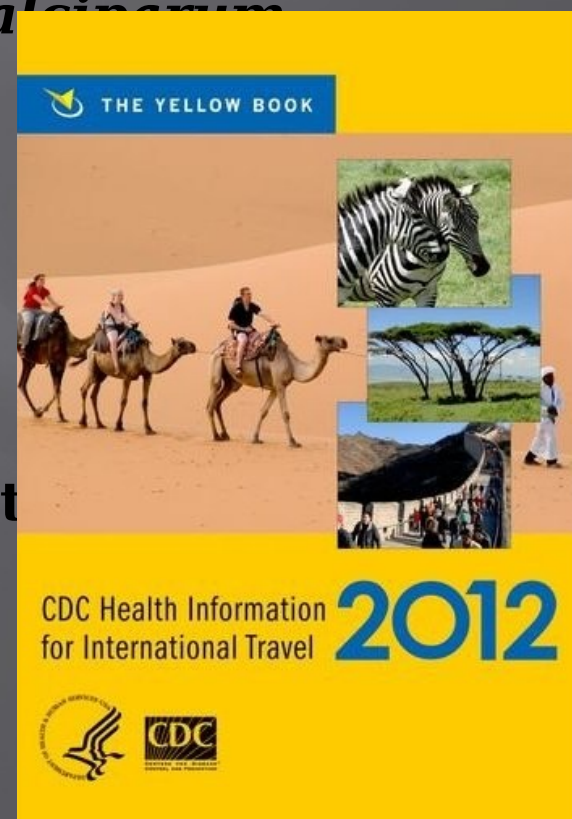


- **Intravenous treatment of severe malaria**
 - Quinidine gluconate
 - Treatment IND with IV Artesunate

- **Oral treatment of uncomplicated *P. falciparum* malaria**
 - Proguanil / atovaquone (Malarone®)
 - Artemether-lumefantrine (Coartem®)
 - Quinine sulfate + doxy or PS
 - Mefloquine (Lariam®)
 - Chloroquine (Aralen®)

- **Available and can be used (Rx adjunct)**
 - Doxycycline, clindamycin, azithromycin

- **Radical cure of relapsing malaria**
 - Chloroquine + primaquine



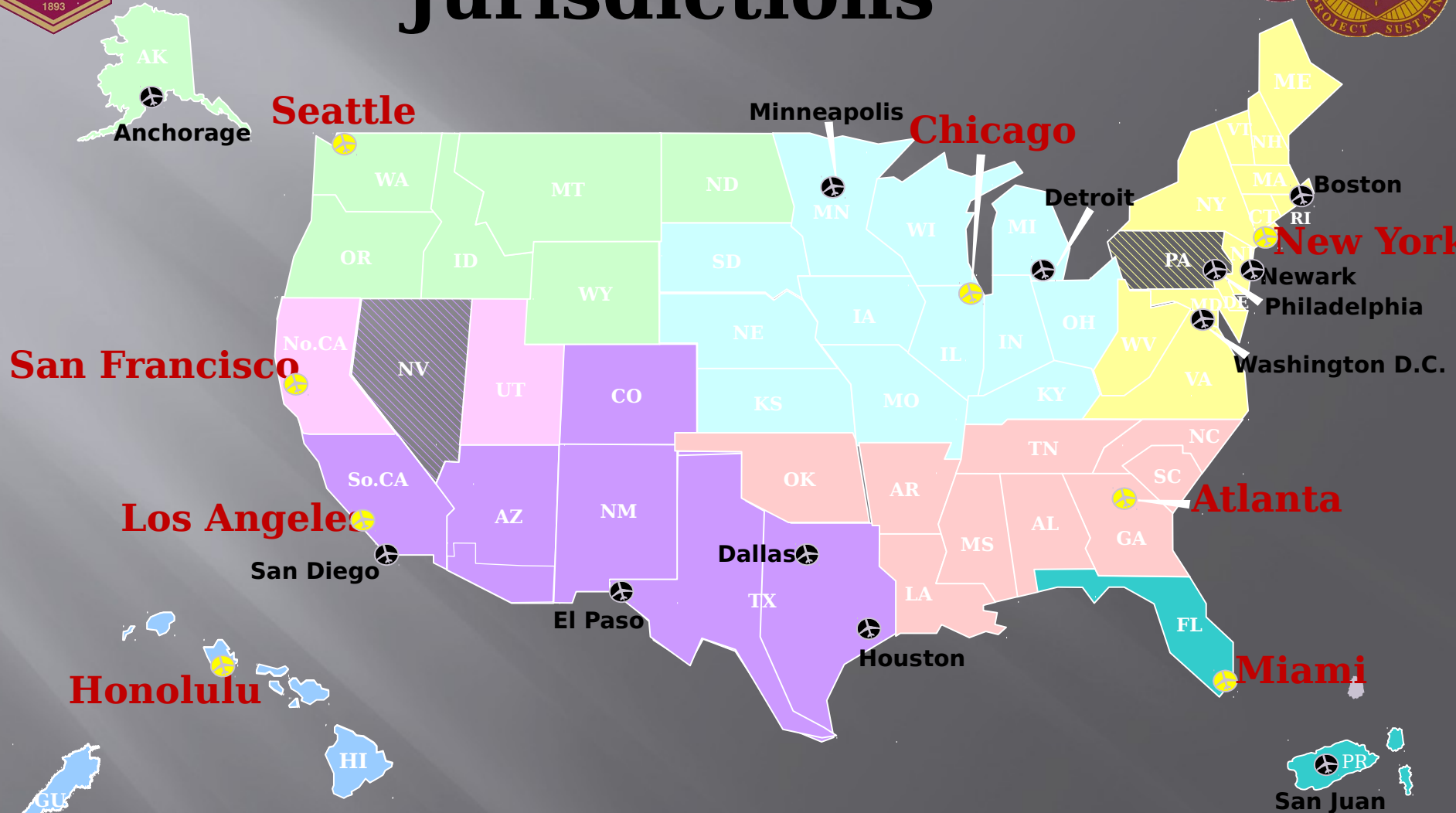


CDC's Compassionate Use IND


- WRAIR produced 1,000 vials of the “clinical lot” for compassionate use (another 10,000 vials being produced now – available in May 2010)
- CDC has a Compassionate Use IND for IV AS
 - Compassionate Use IND went into effect on 21 June, 2007
 - Complete cross-reference to U.S. Army IND for IV AS
 - Administered by Domestic Response Unit & Malaria Branch
 - Announcement Made on 03 August, 2007 in MMWR
- Now released to Canadians, and will be made available in Australia, EU, and elsewhere



CDC Quarantine Stations Jurisdictions

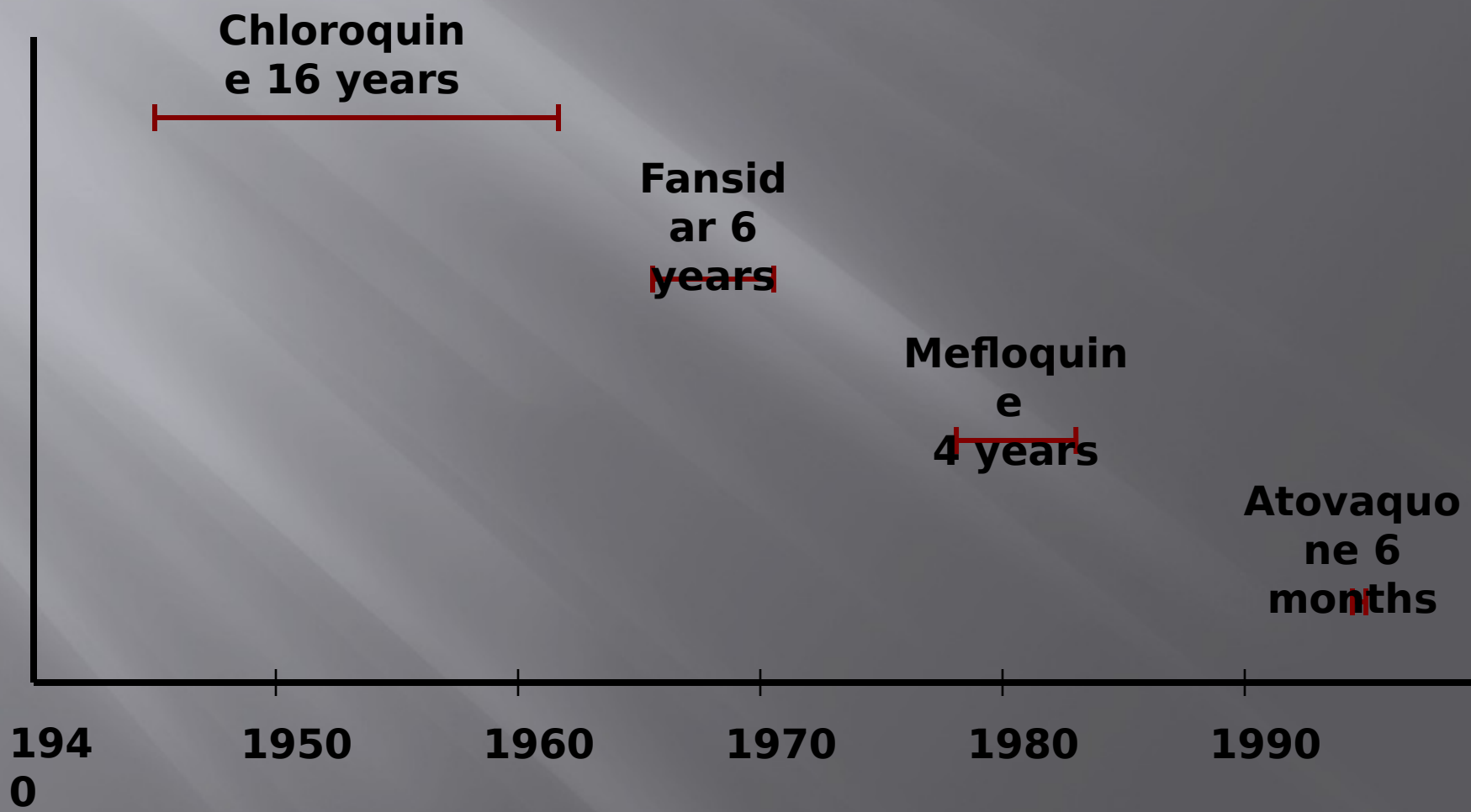


 CDC quarantine station with artesunate

 Additional CDC quarantine stations

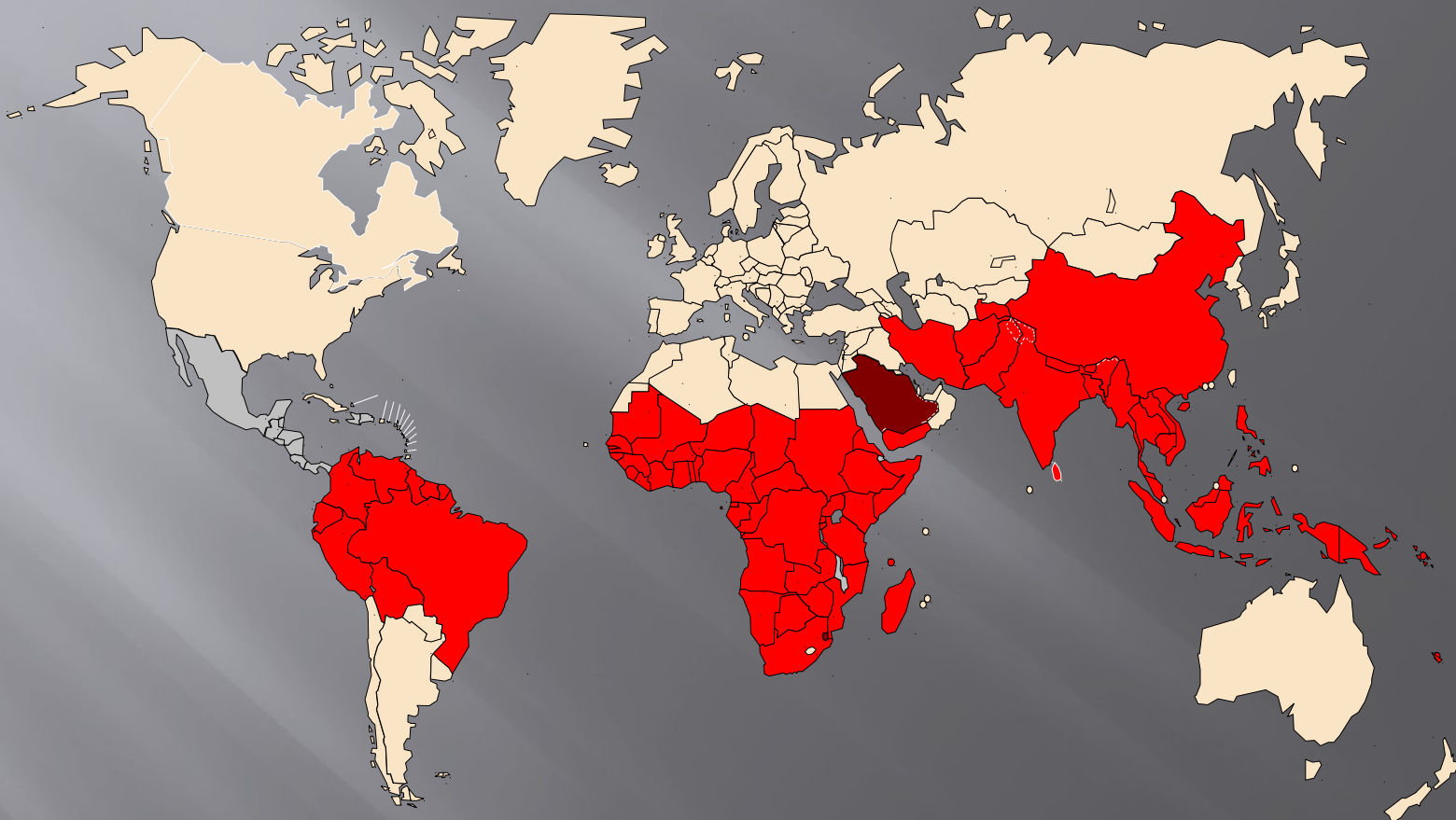


TIME TO DEVELOPMENT OF RESISTANCE ANTIMALARIAL DRUGS





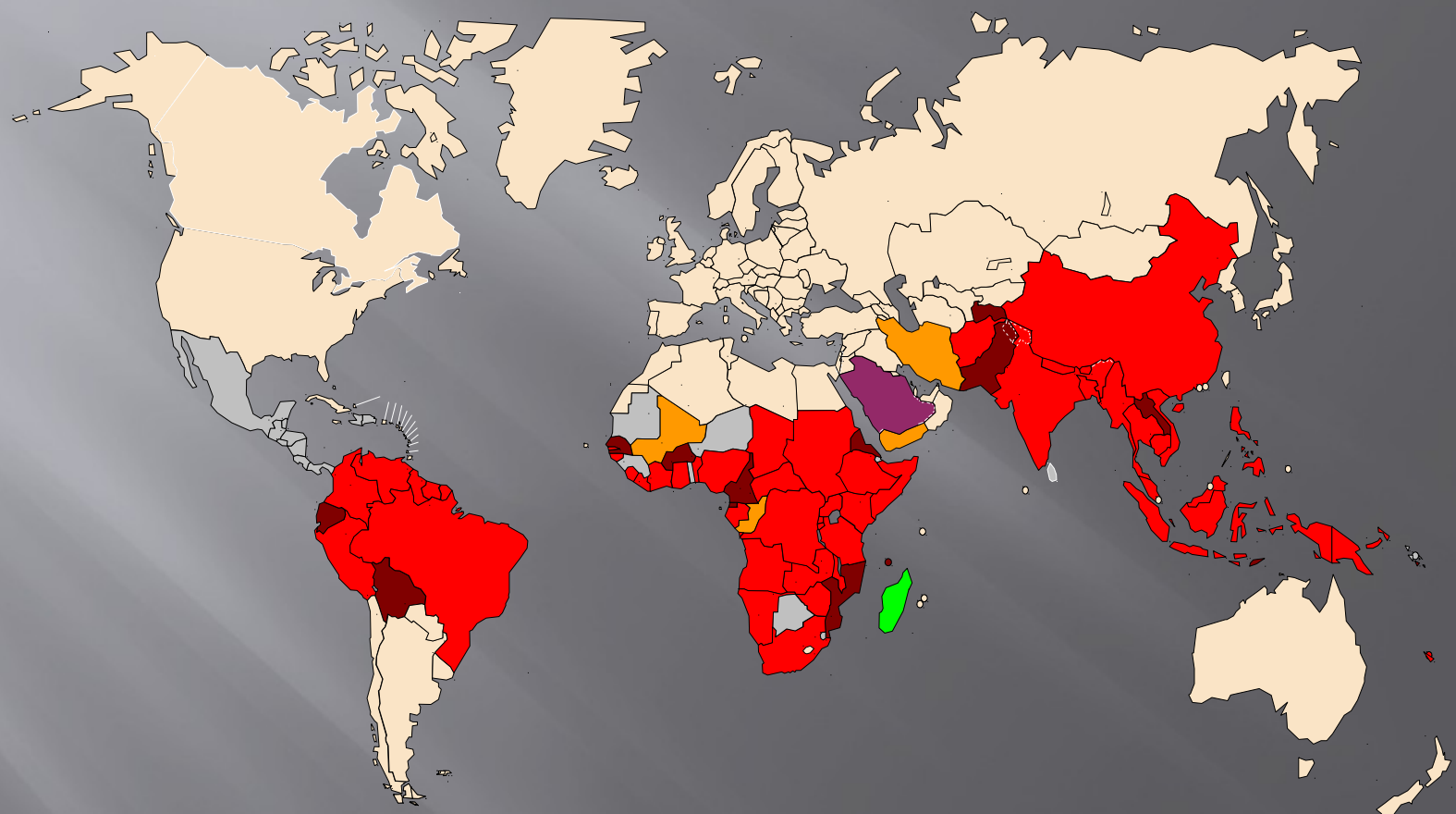
P. falciparum: chloroquine resistance



- Countries with at least one study indicating chloroquine total failure rate $\geq 20\%$
- Countries with at least one study indicating chloroquine total failure rate $\geq 10\%$
- No recent data available



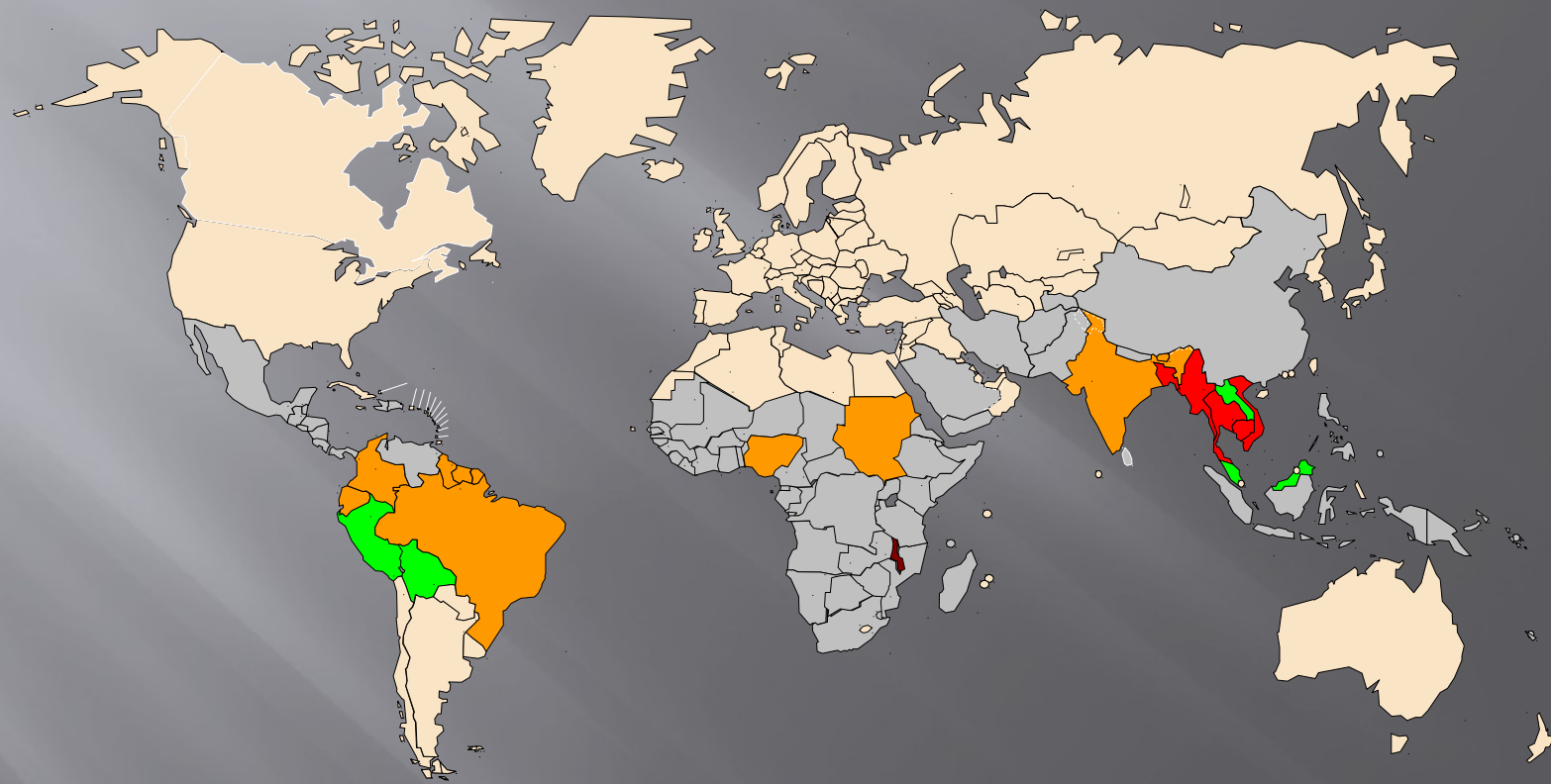
P. falciparum: sulfadoxine-pyrimethamine resistance



- Countries with at least one study indicating sulfadoxine-pyrimethamine total failure rate $\geq 20\%$
- Countries with at least one study indicating sulfadoxine-pyrimethamine total failure rate $\geq 10\%$
- Sulfadoxine-pyrimethamine total failure rate $< 10\%$
- No failure reported
- No recent data available



P. falciparum: mefloquine treatment failure



- Countries with at least one study indicating mefloquine total failure rate $\geq 20\%$
- Countries with at least one study indicating mefloquine total failure rate $\geq 10\%$
- Mefloquine total failure rate $< 10\%$
- No failure reported
- No recent data available



P. vivax: chloroquine prophylaxis or treatment failure



P. vivax prophylactic or treatment failure



Evidence of Artemisinin-Resistant Malaria in Western Cambodia

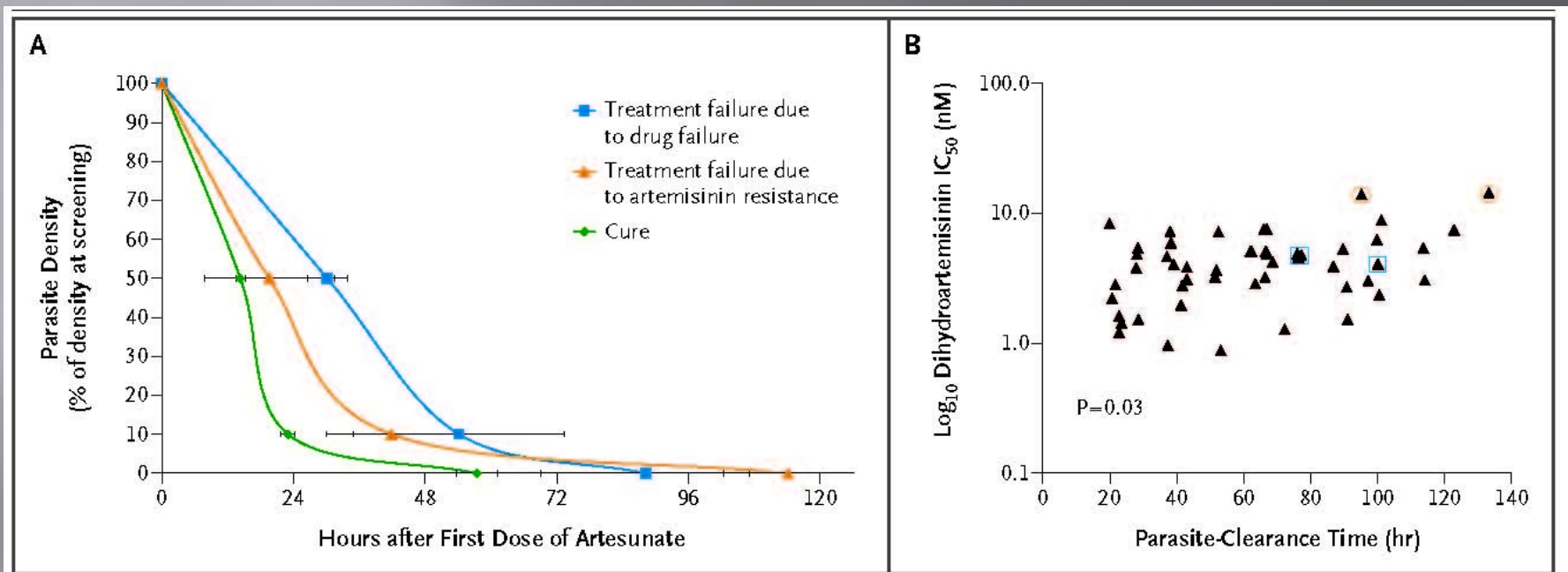


Figure 1. Parasite Density, Parasite-Clearance Time, and 50% Inhibitory Concentration (IC₅₀) among Patients Receiving Artesunate, According to Clinical Outcome.

Panel A shows the parasite-reduction curves for the 56 patients who were cured, the 2 patients classified as having artemisinin-resistant infections, and the 2 with drug failures (i.e., patients who had recrudescence but who were not classified as having artemisinin-resistant infection, since the drug level was inadequate). The data points and horizontal I bars denote the means and standard errors. Panel B shows the parasite-clearance times in the artesunate group, as compared with the IC₅₀ for dihydroartemisinin (R=0.31, P=0.03). Orange circles indicate patients whose infection was classified as artemisinin-resistant, and blue squares patients in whom treatment failed but whose infection was not classified as resistant.



DRUG

PROBLEMS

Artemisinin	Recrudescence, Neurotoxicity
Atovaquone	Resistance
Azithromycin	Limited efficacy
Chloroquine	Resistance
Doxycycline	Phototoxicity, GI intolerance
Fansidar	Resistance, Allergic Rxns
Halofantrine	Cardiotoxicity
Mefloquine	Resistance, Psychiatric effects
Primaquine	Narrow Therapeutic Index
Proguanil	Resistance, Mouth ulcers
Quinidine gluconate	Going off the market?
Quinine	Resistance, Tinnitus

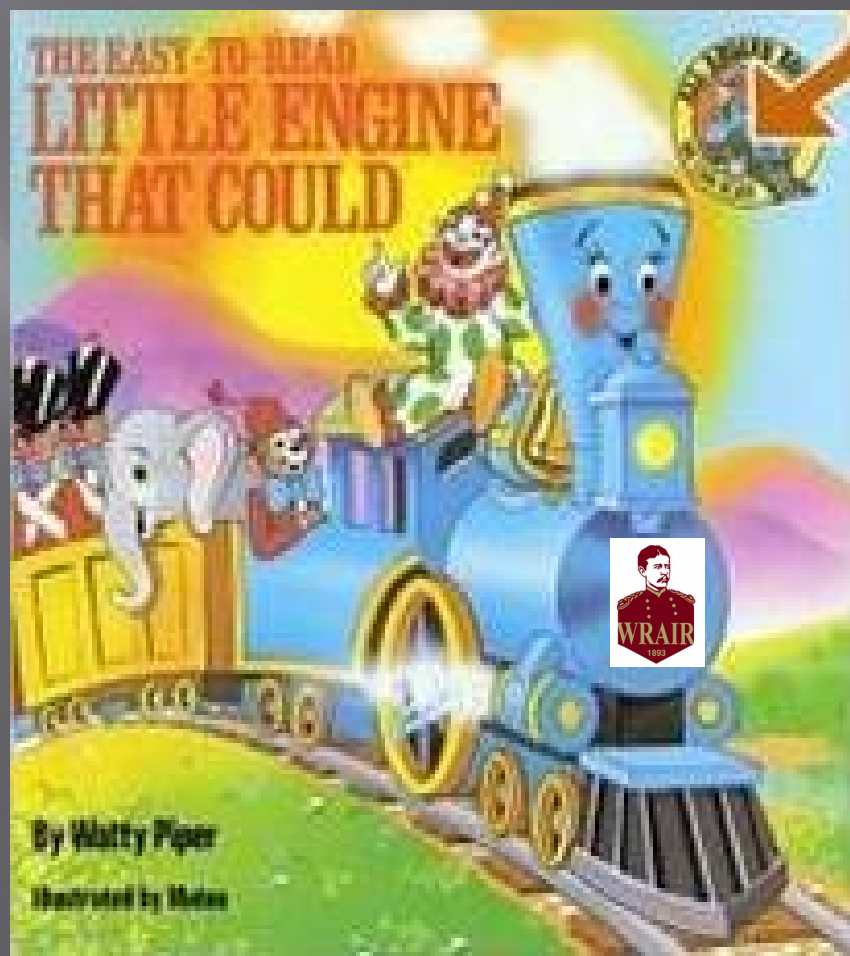


DoD Antimalarial Drug Program

The Biggest Little Drug Company in the World

➤ Filed 63 IND's with US FDA

- Chloroquine
- Primaquine
- C-P Tablets
- Mefloquine
- Doxycycline
- Halofantrine
- Fansidar
- Malarone
- IV Artesunate





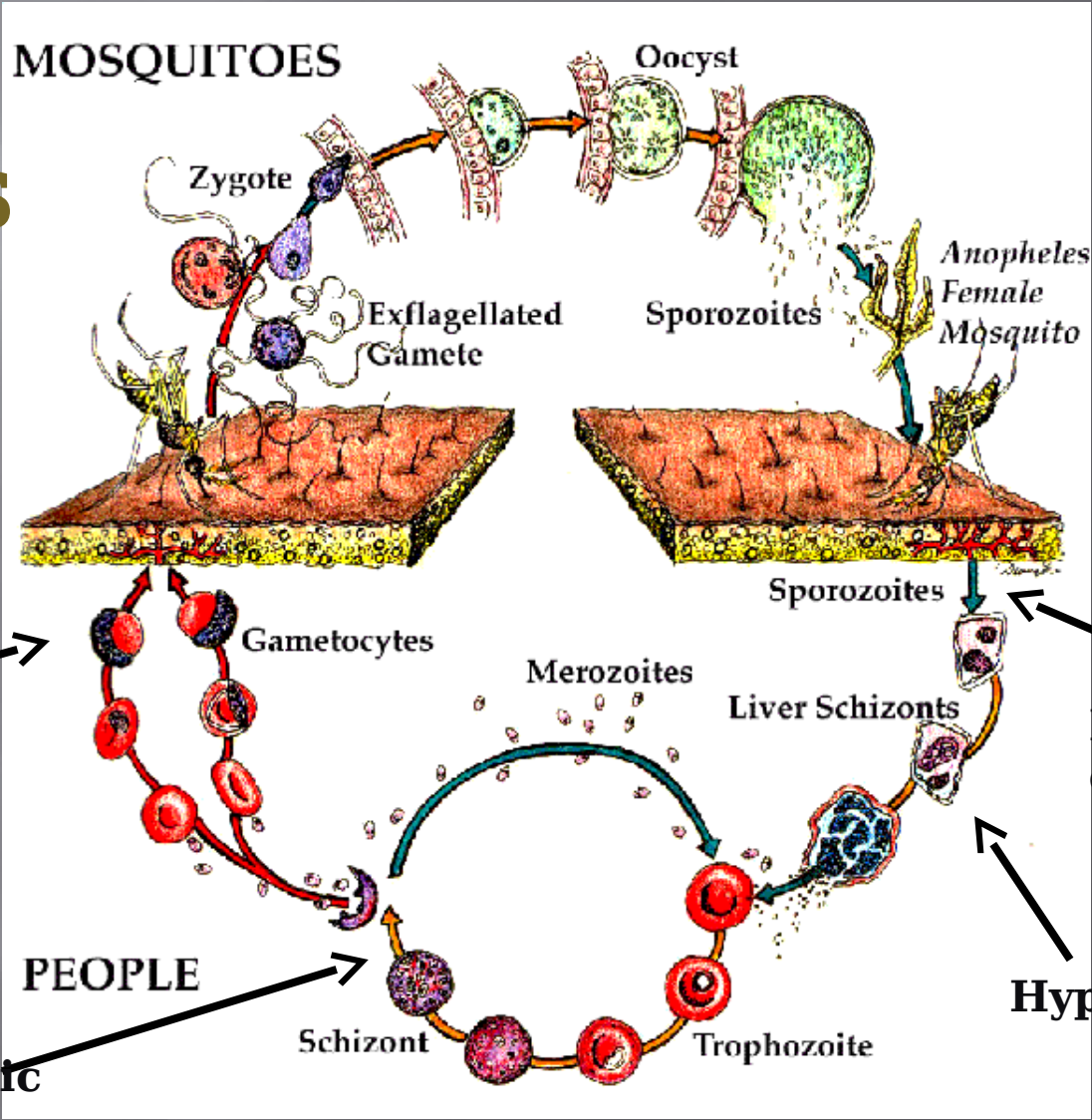
\$300-500 Million per Candidate

Clinical Trials

	Preclinical Testing	File IND at FDA	Phase I	Phase II	Phase III	File NDA at FDA	FDA		Phase IV
Years	3.5		1	2	3		2.5	12 Total	Additional Post marketing testing required by FDA
Test Population	Laboratory and animal studies		20 to 80 healthy volunteers	100 to 300 patient volunteers	1000 to 3000 patient volunteers		Review process / Approval		
Purpose	Assess safety and biological activity		Determine safety and dosage	Evaluate effectiveness, look for side effects	Verify effectiveness, monitor adverse reactions from long-term use				
Success Rate	5,000 compounds evaluated		5 enter trials					1 approved	



Vaccines



Transmission Blocking

Pre-erythrocytic

Erythrocytic

Hyponozoite



Approaches to Control

- Vector Control Methods
 - Breeding site control, larvacide, adulticide, bed nets and personal protection
- Treatment Strategies
 - Passive case finding and self-referral
 - Home treatment early in course of disease
 - Prophylaxis in selected groups



Controversies in Malaria

- **Prophylaxis... drug to use?**
 - Mefloquine vs. Malarone vs. Doxycycline
- **Prophylaxis... to do or not?**
 - Short-term vs. Long-term Deployments
- **Prophylaxis... duration?**
 - Continuous vs. Interrupted
- **RDTs...**



Malaria

Take Home Points

- Malaria continues to evolve, not just in resistance, but in new species
- Malaria is as important a consideration for force health protection today as ever
- Malaria is not just a force health protection issue, but a strategic stability operations consideration in the global war on terrorism
- We have more tools today than ever, but we can lose them at any time and we must understand and respect their limitations



Reality - Case study



- 45 y/o Male from Ivory Coast. Lived there 20 yrs ago and now owns property and visits every few years
- Last visit 2008 and took prophylaxis. Went this year from Feb to mid-Mar and had an uneventful stay but did not take prophylaxis
- Returned 15Mar and on the 24th or so got fevers/chills and rigors
- Used OTCs 1 day, had syncope while at work
- Civ ER via EMS on the 26th. Labs sig only for platelets 60s and dx falciparum malaria by giemsa with 0.7% parasitemia
- Give him a script of oral quinine and doxycycline. He took doxycycline but was unable to fill oral quinine due to pharmacy availability (cost)
- On the 28th felt worse. Parasitemia now 0.5% and labs the same with platelet 46 main abnormal other than mild prerenal azotemia
- Response to malarone po first 24hr in ICU and d/c after 3rd day
- 14d of primaquine given due to overabundance of caution. Seen Monday and he was doing well



These Men
DIDN'T
TAKE THEIR

DOXYCYCLINE





Questions?